REMARKS

All the claims previously of record have now been canceled and replaced with new claims 112-162. Claims 112, 128, and 144 are each directed to a composition of matter comprising L-carnitine and an agent to increase blood plasma/serum insulation concentration. Claims 112, 128 and 144 differ in their preamble and in the manner in which they define the relationship between the amount of the agent and the amount of L-carnitine. In addition, claim 144 specifies the amount of the agent by reference to its efficacy to increase blood plasma/serum insulin concentration above a specified level.

The wording in claims 112 and 128 regarding promoting muscle carnitine accumulation in human skeletal muscle is supported by the sentence starting at page 17, line 25 of the specification.

The claims as originally filed refer to a carnitine substance whereas the new independent claims all refer to L-carnitine. Support for limitation to L-carnitine is provided throughout the specification as originally filed. For example, page 7 lines 15-17 and examples I and II emphasize L-carnitine.

The original claims refer to increasing blood plasma insulin concentration, whereas the new independent claims refer to increasing blood plasma/serum insulin concentration. Support for this change in terminology is provided by the emphasis on serum insulin concentrations at page 16, lines 6-7 of the specification.

Claim 112 specifies that "the amount by weight of said agent is at least ten times the amount by weight of said L-carnitine". Support for this limitation is set out, for example, on page 5, from line 20. In the various ranges set out at page 5, lines 20-24, the value for the lower end of the range remains unchanged at 10 in each case. Similarly, the examples at page 5, lines 25 to 28 refer back to 0.25 grams of the carnitine substance and describe various ranges, each of which has a lower limit at 2.5 grams of the agent, that is, ten times the amount by weight of the carnitine substance. Thus, throughout this passage, it can be seen that no examples have a ratio below 10.

Claim 128 is otherwise based on claim 71 in combination with claim 58.

Claim 144 includes the requirement that the insulin concentration is increased above 50mU/l. Support for this limitation is set forth at page 14, line 27, in conjunction with the passage at page 16, lines 1 to 6. At page 16, plasma carnitine concentration is described as lower (because of retention) "than during a 5 and 30 mU. m^{-2} . min^{-1} insulin clamp". Referring back to page 14, line 26 and 27, the 5 and 30 mU . m^{-2} . min^{-1} insulin infusion protocols lead to serum insulin concentrations of 10.3 ± 0.3 and 47.8 ± 1.3, respectively. Thus, page 16 distinguishes between the 5 and 30 protocols, and higher concentrations achieved. Noting that the value of 47.8 ± 1.3 extends to a value of 49.1, there is support for a claim to increase insulin concentration above 50mU/l.

As indicated above, each of the independent claims 112, 138 and 124 refers to an agent to increase blood plasma/serum insulin concentration. The agent, as defined, may be a single material or more than one material. For example, page 18, lines 4 and 5 describe the use of "other agents" (other than those specifically described earlier), which may be used "as an alternative or as an addition". Original claims 10 and 11 (at least) also refer to the agent (singular) comprising combinations of materials. Furthermore, page 7, line 19 explains that the agent can be "anything which acts to increase insulin concentration". Accordingly, the term "agent" in the independent claims (and in the dependent claims except to the extent that the context indicates otherwise) is to be interpreted as covering single materials or combinations of materials as the agent, the single material or the combination being present in the amounts required by the claims.

Claim 160 is based on claim 93, now with specific reference to claim 112. Claim 161 represents the prepared human dose to be administered in the method of claim 160, and again refers specifically to claim 112. Claim 162 broadly corresponds with claim 160, referring to "carnitine deficiency" rather than "carnitine retention". Problems relating to carnitine deficiency are mentioned in the second paragraph of the application, for example.

The examiner rejected claim 58 based on the term "carnitine substance". This term has now been replaced by "L-carnitine" and applicant submits that the bounds of the claim are clearly set forth.

The examiner rejected claim 65 based on the term "simple", as part of the phrase "simple carbohydrate". The examiner would apparently accept replacing "simple carbohydrate" by "mono-disaccharides". The corresponding new claims 117, 133, and 149 refer to "mono-disaccharides."

The rejection over the prior art raised in the Office action of April 27, 2009 are based on Davis, Pola, Bohles and Gross. Referring to these documents in turn, applicant comments as follows.

Davis discloses various example compositions which include a carnitine substance. In each of seven examples (pages 5 and 6), no component of the composition is present at a level more than about four times the amount of L-carnitine. Claim 112 requires "the amount by weight of said agent is at least ten times the amount by weight of said L-carnitine". Therefore, claim 112 is novel over Davis. Claims 160-162 are therefore novel over Davis.

Davis describes administering the compositions by means of the digestive tract ("through the intestinal wall and also sublingually in humans") (page 7, line 6). Administration in this manner will have no effect on insulin concentration, because insulin is not present in the intestinal lumen. The compositions of Davis cannot increase blood plasma/serum insulin concentration. Consequently, claim 128 is novel in requiring "an agent to increase blood plasma/serum insulin concentration". Claim 144 is novel in requiring "the agent is present in an amount sufficient to increase blood plasma/serum insulin concentration above 50mU/l".

Accordingly, the independent claims 128 and 144 are novel over Davis.

Pola also describes various compositions including L-carnitine (pages 6 to 9). In no case is any other constituent present at a level of more than ten times the amount by weight of L-carnitine. Claim 112 is novel by requiring "the amount by weight of said agent is at least ten times the amount by weight of said L-carnitine". Claims 160-162 are therefore novel over Pola.

Pola makes no reference to insulin. Pola therefore does not disclose any increase in insulin concentration. Therefore, claim 128 is novel in requiring "an agent to increase blood plasma/serum insulin concentration". Claim 144 is novel in requiring "the agent is present in an amount sufficient to increase blood plasma/serum insulin concentration above 50mU/l".

Accordingly, the independent claims 128 and 144 are novel over Pola.

Bohles is directed to the use of L-carnitine supplementation (see "conclusions" on page 12), to influence other metabolic effects. Thus, it is the L-carnitine which is the mechanism used to achieve another effect. Bohles does not address the issue of L-carnitine accumulation in human skeletal muscle. Furthermore, insulin concentrations differ only by statistically non-significant amounts during the procedures described by Bohles (see table II, particularly the heading and the figures for insulin). Thus, table II shows clearly that no compositions or combinations of compositions administered by Bohles have the effect of increasing blood plasma/serum insulin concentration. Consequently, it follows that Bohles does not disclose a composition according to claim 112, in which the "weight of the said agent is at least ten times the amount by weight of said L-carnitine". Claims 112 and 160-162 are novel over Bohles.

Bohles does not disclose insulin concentration being boosted, as noted above. Consequently, claim 128 is novel by requiring "an agent to increase blood plasma/serum insulin concentration" and claim 144 is novel by requiring "the agent is present in an amount sufficient to increase blood plasma/serum insulin concentration above 50 mU/l."

Accordingly, the independent claims are novel over Bohles.

Gross relates solely to intestinal absorption of carnitine (note that the title refers to "by the rodent's small intestine"). Gross is silent in relation to carnitine in human skeletal muscle. The experimental technique described by Gross (page 226, second column, line 4) describes placing L-carnitine in the lumen of subject intestine via a syringe. There is no reference to the introduction of any composition comprising L-carnitine and agent, nor is there any reference to insulin. Specifically, there is no reference to the use of any agent as part of a composition with L-carnitine, nor that the agent should be capable of increasing blood plasma/serum insulin, nor that the amount by weight of the agent should be at least ten times the amount by weight of L-carnitine. Furthermore, Gross infers that insulin plays a role (not defined) in the regulation of carnitine transport in perfused liver, by referring to previous work by Kispal et al (Biochem Biophy Acta 1987). However, inspection of the latter reference shows that insulin would reduce liver carnitine uptake, which is contrary to applicant's contention that insulin, especially at concentration above 50mU/ml plasma, increases muscle carnitine uptake. Accordingly, claims 112 and 160-162 are novel over Gross.

Gross describes no agent present in the composition along with L-carnitine, as noted above, nor makes any reference to insulin concentration. Consequently, there is no disclosure in Gross of the requirement for "an agent to increase blood plasma/serum insulin concentration" or "to increase blood plasma/serum insulin concentration above 50mU/l". Accordingly, claims 128 and 144 are novel over Gross.

In view of the foregoing, the independent claims 112, 128 and 144 are novel over Gross.

None of the prior art references sets out the suggestion that stimulating an increase in insulin levels within the blood plasma/serum, in the presence of L-carnitine, can be used to promote muscle carnitine accumulation in human skeletal muscle. Davis and Gross deal with intestinal absorption of carnitine, as noted above, so that insulin concentrations are not relevant issues, as insulin will not be present in the intestinal lumen. Consequently, there is

no suggestion in either of these references as to how carnitine can be managed within skeletal muscles.

In relation to Pola, none of the various compositions described contains sufficient quantities of other agents to have any measurable effect on plasma insulin concentration. As noted (and as now defined in claim 144), it is desirable to increase insulin above about 50mU/l in order for any increase in muscle carnitine retention to be observed (see Fig. 6 of the present application), but this level (50mU/l) is far in excess of anything which would be achieved by the compositions described by Pola. Moreover, it is to be noted that Pola does not describe the agents as being for this purpose, which is not surprising given that they would not achieve this purpose. It is therefore clear that Pola is unaware or indifferent to the issue of increasing insulin sufficiently to promote carnitine accumulation and consequently, makes no suggestion of this to the reader.

Finally, Bohles indicates that there is no statistical difference between the insulin levels in each of the three study periods and therefore any effect on carnitine retention achieved during the experiments cannot be attributable to insulin. Indeed, Bohles attributes the changes in carnitine levels to regulatory activities of the kidney. Again, there is no information in Bohles in relation to the retention of carnitine in skeletal muscle, nor any disclosure, recognition or suggestion that this can be promoted by achieving high levels of insulin concentration.

Accordingly, none of these prior art references have considered or suggested the approach which lies behind the present claimed subject matter, namely to promote high levels of insulin concentration by the use of an appropriate agent, while in the presence of L-carnitine. The desirable high level is a feature of each of the claims, being expressed as "at least ten times the amount by weight of said L-carnitine" (claims 112 and 160-162), as particular values (claim 128) and by reference to the achieved insulin concentrations (claim 144). For all these reasons, applicant submits that the claimed subject matter is not disclosed or suggested by the references previously cited, whether taken singly or in

combination. Therefore, the independent claims are patentable and it follows that the dependent claims also are patentable.

Respectfully submitted,

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